

P A N T COOPERATION TREATY

PCT
NOTIFICATION OF ELECTION
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 31 October 2000 (31.10.00)	
International application No. PCT/US00/05582	Applicant's or agent's file reference 175953
International filing date (day/month/year) 03 March 2000 (03.03.00)	Priority date (day/month/year) 05 March 1999 (05.03.99)
Applicant BOYD, Michael, R.	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

05 October 2000 (05.10.00)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Diana Nissen Telephone No.: (41-22) 338.83.38
---	--

PCT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 175953	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 05582	International filing date (day/month/year) 03/03/2000	(Earliest) Priority Date (day/month/year) 05/03/1999
Applicant THE UNITED STATES OF AMERICA, represented by THE S		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
 - contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of invention is lacking (see Box II).

4. With regard to the **title**,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-11,19-29

Present claims 1-11,19-29 relate to a method and composition defined by reference to the following term : vacuolar-type (H⁺)-ATPase. The use of this term in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the parts relating to the method and composition mentioned in the description at pages 20-21.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/05582

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/365 A61P35/00 A61P35/04 A61P15/08 A61P19/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GALINIS L DEBORAH ET AL: "Lobatamides A and B. Novel Cytotoxic Macrolides from the Tunicate Aplidium lobatum" JOURNAL OF ORGANIC CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY, EASTON, vol. 62, no. 26, 1997, pages 8968-8969, XP002111864 ISSN: 0022-3263 page 8968, left-hand column ---- -/-	1, 17, 19, 35

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

8 December 2000

Date of mailing of the international search report

21/12/2000

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Voyiazoglou, D

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/05582

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
X	ERICKSON L ET AL: "Salicylihalamides A and B, Novel Cytotoxic Macrolides from the Marine Sponge <i>Haliclona</i> sp" JOURNAL OF ORGANIC CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. EASTON, vol. 62, no. 23, 1997, pages 8188-8192, XP002111863 ISSN: 0022-3263 page 8191, left-hand column; examples 1,2 ---	1,17,19, 35
X	WO 99 05136 A (PANNELL LEWIS ;BEUTLER JOHN A (US); BOYD MICHAEL R (US); ERICKSON) 4 February 1999 (1999-02-04) cited in the application claims 1,7,18 ---	1,17,19, 35
X	K. A. DEKKER ET AL : "Novel lactone compounds from <i>Mortierella verticillata</i> that induce the human low density lipoprotein receptor gene: fermentation, isolation, structural elucidation and biological activities" JOURNAL OF ANTIBIOTICS., vol. 51, no. 1, 1998, pages 14-20, XP000971100 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820 cited in the application page 14, left-hand column; figure 1 ---	1,19
X	JIN WOO KIM ET AL: "Oximidines I and II: Novel antitumor macrolides from <i>Pseudomonas</i> sp." JOURNAL OF ORGANIC CHEMISTRY., vol. 64, no. 1, 1999, pages 153-155, XP000971102 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 cited in the application page 153, left-hand column, line 1 - line 7; figure 1 ---	1,17,19, 35
A	KEN-ICHI SUZUMURA ET AL: "Structural elucidation of YM-75518, a novel antifungal antibiotic isolated from <i>Pseudomonas</i> sp.Q38009" TETRAHEDRON LETTERS, vol. 38, no. 43, 1997, pages 7573-7576, XP002154892 OXFORD GB figure 1 -----	1,17,19, 35

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-11,19-29

Present claims 1-11,19-29 relate to a method and composition defined by reference to the following term : vacuolar-type (H+)-ATPase. The use of this term in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the parts relating to the method and composition mentioned in the description at pages 20-21.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No

PCT/US 00/05582

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9905136 A	04-02-1999	AU EP	8501598 A 1000053 A	16-02-1999 17-05-2000

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 September 2000 (08.09.2000)

PCT

(10) International Publication Number
WO 00/51589 A3

- (51) International Patent Classification⁷: **A61K 31/365.** (A61P 35/00, 35/04, 15/08, 19/10)
- (21) International Application Number: **PCT/US00/05582**
- (22) International Filing Date: 3 March 2000 (03.03.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/122,953 5 March 1999 (05.03.1999) US
60/169,564 8 December 1999 (08.12.1999) US
- (71) Applicant (*for all designated States except US*): THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; National Institutes of Health, Office of Technology Transfer, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852 (US).
- (72) Inventor; and
- (75) Inventor/Applicant (*for US only*): BOYD, Michael, R. [US/US]; 5217 Fairgreen Way, Ijamsville, MD 21754 (US).
- (74) Agents: LARCHER, Carol et al.; Leydig, Voit & Mayer, Ltd., Suite 4900, Two Prudential Plaza, 180 North Stetson, Chicago, IL 60601-6780 (US).
- (81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

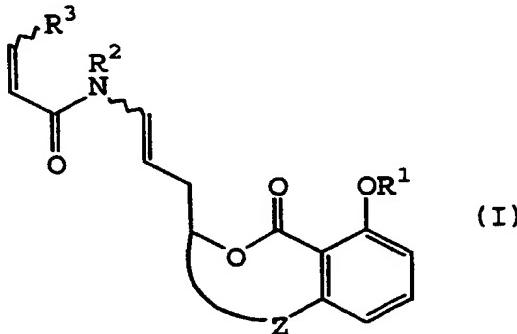
— With international search report.

(88) Date of publication of the international search report:
12 July 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: VACUOLAR-TYPE (H⁺)-ATPase-INHIBITING COMPOUNDS, COMPOSITIONS, AND USES THEREOF

WO 00/51589 A3



(57) Abstract: The present invention provides vacuolar-type (H⁺)-ATPase-inhibiting compounds, compositions thereof, and methods of using them to treat or prevent a condition treatable by the inhibition of a vacuolar-type (H⁺)-ATPase. The composition of the present invention comprises a compound of the present invention and a carrier. The method of the present invention includes administering a vacuolar-type (H⁺)-ATPase inhibiting-effective amount of a compound of the present invention. The compound of the present invention has formula (I) wherein R¹ and R² are H, saturated or unsaturated alkyl, aryl, R⁶CH₂, R⁶CO-, or R⁶SO₂-, wherein R⁶ is H, saturated or unsaturated alkyl, or aryl; R³ is H, alkyl, aryl, an oxime, or an oxime methyl ether; the aromatic ring is unsubstituted or substituted; and Z is a contiguous linker comprising a chain of 0-10 atoms which, together with the five atoms beginning with the carbon of the aromatic ring in meta-relationship with OR¹ and ending with the carbon directly attached to the alkyl oxygen of the lactone, integrally form a 5-17 membered ring; or a pharmaceutically acceptable salt, an ester, or a prodrug thereof.

INTERNATIONAL SEARCH REPORT

Inten:	Application No
PCT/US 00/05582	

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	A61K31/365	A61P35/00	A61P35/04	A61P15/08	A61P19/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GALINIS L DEBORAH ET AL: "Lobatamides A and B. Novel Cytotoxic Macrolides from the Tunicate <i>Aplidium lobatum</i> " JOURNAL OF ORGANIC CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY, EASTON, vol. 62, no. 26, 1997, pages 8968-8969, XP002111864 ISSN: 0022-3263 page 8968, left-hand column ---	1, 17, 19, 35 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

8 December 2000

Date of mailing of the international search report

21/12/2000

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patenttaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax (+31-70) 340-3016

Authorized officer

Voyiazoglou, D

INTERNATIONAL SEARCH REPORT

Interinal Application No

PCT/US 00/05582

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ERICKSON L ET AL: "Salicylihalamides A and B, Novel Cytotoxic Macrolides from the Marine Sponge <i>Haliclona</i> sp" JOURNAL OF ORGANIC CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. EASTON, vol. 62, no. 23, 1997, pages 8188-8192, XP002111863 ISSN: 0022-3263 page 8191, left-hand column; examples 1,2 ---	1,17,19, 35
X	WO 99 05136 A (PANNELL LEWIS ;BEUTLER JOHN A (US); BOYD MICHAEL R (US); ERICKSON) 4 February 1999 (1999-02-04) cited in the application claims 1,7,18 ---	1,17,19, 35
X	K. A. DEKKER ET AL : "Novel lactone compounds from <i>Mortierella verticillata</i> that induce the human low density lipoprotein receptor gene: fermentation, isolation, structural elucidation and biological activities" JOURNAL OF ANTIBIOTICS., vol. 51, no. 1, 1998, pages 14-20, XP000971100 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820 cited in the application page 14, left-hand column; figure 1 ---	1,19
X	JIN WOO KIM ET AL: "Oximidines I and II: Novel antitumor macrolides from <i>Pseudomonas</i> sp." JOURNAL OF ORGANIC CHEMISTRY., vol. 64, no. 1, 1999, pages 153-155, XP000971102 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 cited in the application page 153, left-hand column, line 1 - line 7; figure 1 ---	1,17,19, 35
A	KEN-ICHI SUZUMURA ET AL: "Structural elucidation of YM-75518, a novel antifungal antibiotic isolated from <i>Pseudomonas</i> sp.Q38009" TETRAHEDRON LETTERS, vol. 38, no. 43, 1997, pages 7573-7576, XP002154892 OXFORD GB figure 1 -----	1,17,19, 35

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-11,19-29

Present claims 1-11,19-29 relate to a method and composition defined by reference to the following term : vacuolar-type (H+)-ATPase. The use of this term in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the parts relating to the method and composition mentioned in the description at pages 20-21.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. Application No

PCT/US 00/05582

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9905136 A	04-02-1999	AU 8501598 A EP 1000053 A	16-02-1999 17-05-2000

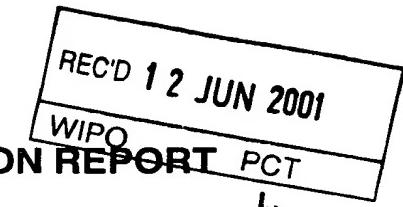
K 091914708 -

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



14

Applicant's or agent's file reference 175953	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/05582	International filing date (day/month/year) 03/03/2000	Priority date (day/month/year) 05/03/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
<p>Applicant THE UNITED STATES OF AMERICA, represented by THE S</p> <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 16 sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		

Date of submission of the demand 05/10/2000	Date of completion of this report 08.06.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Markopoulos, E Telephone No. +49 89 2399 8658



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/05582

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-16,18-91	as originally filed	
17	with telefax of	11/04/2001

Claims, No.:

1-31	with telefax of	11/04/2001
------	-----------------	------------

Drawings, sheets:

1/14-14/14	as originally filed
------------	---------------------

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/05582

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:
5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
see separate sheet
6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- the entire international application.
- claims Nos. 1-17 in respect of industrial applicability; and 1-11, 19-24 in regard of inventive step.
- because:
- the said international application, or the said claims Nos. 1-17 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. 1-11, 19-24.
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- the written form has not been furnished or does not comply with the standard.
- the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/05582

1. Statement

Novelty (N)	Yes:	Claims 1-17, 19 (new), 20, 22-30
	No:	Claims 19 (originally filed), 21
Inventive step (IS)	Yes:	Claims - (see III)
	No:	Claims 12-17, 25-30
Industrial applicability (IA)	Yes:	Claims 19 (originally filed), 19 (new), 20-30
	No:	Claims -

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/05582

Re Item I

Basis of the report

The amendments concerning claims 18 (originally filed claim 19) and new claim 31 have not been taken into account since they contain subject-matter which go beyond the content of the application as filed (Art. 34 (2b) PCT).

Concerning the admissibility of a disclaimer, it has to be stated that a disclaimer can only be used by way of exception for avoiding claim anticipation.

Regarding the proviso in claims 18 and 31, there is no basis for disclaiming apicularen A and B in the prior art at hand. Since the exclusion in form of a disclaimer is an exceptional case applied when there is an accidental novelty-destroying disclosure and since the excluded subject-matter is said to contribute to the solution of the problem (p. 17 of the description), the present disclaimer is not acceptable.

Concerning the disclaimer in claim 1, the following has to be mentioned:

The disclaimer formulated on the basis of a certain disclosure is only allowable if the cited document containing the said disclosure has no relevance for any further examination of the claimed invention and it must then disappear from the prior art field to be taken into consideration.

In the present case, documents D1, D2, and D5 disclose substances having anti-cancer activity. Since no document states an effect by inhibiting vacuolar-type (H⁺) ATPase and there seems to be no link as to this inhibition and the action mode of the screened substances in D1, the amendment in new claim 1 is regarded as acceptable.

However, if in the national phase it can be proven that the above mentioned documents relate to the same field as that of the claimed invention, the disclaimer in claim 1 will not be allowed because the subject-matter to be disclaimed will be considered relevant to the assessment of inventive step.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. In view of the restricted search it is not at present possible to carry out a full examination of the application (Rule 66.1(e) PCT). This applies for the assessment of inventive step of

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/05582

originally filed independent claim 19 and new claims 1-11 and 19-24.

2. Claims 1-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: WO 99 05136 A (PANNELL LEWIS ;BEUTLER JOHN A (US); BOYD MICHAEL R (US); ERICKSON) 4 February 1999 (1999-02-04) cited in the application

D2: GALINIS L DEBORAH ET AL: 'Lobatamides A and B. Novel Cytotoxic Macrolides from the Tunicate Aplidium lobatum' JOURNAL OF ORGANIC CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. EASTON, vol. 62, no. 26, 1997, pages 8968-8969, XP002111864 ISSN: 0022-3263

D3: ERICKSON L ET AL: 'Salicylihalamides A and B, Novel Cytotoxic Macrolides from the Marine Sponge Haliclona sp' JOURNAL OF ORGANIC CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. EASTON, vol. 62, no. 23, 1997, pages 8188-8192, XP002111863 ISSN: 0022-3263

D4: K. A. DEKKER ET AL : 'Novel lactone compounds from Morterella verticillata that induce the human low density lipoprotein receptor gene: fermentation, isolation, structural elucidation and biological activities' JOURNAL OF ANTIBIOTICS., vol. 51, no. 1, 1998, pages 14-20, XP000971100 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820 cited in the application

D5: JIN WOO KIM ET AL: 'Oximidines I and II: Novel antitumor macrolides from Pseudomonas sp.' JOURNAL OF ORGANIC CHEMISTRY., vol. 64, no. 1, 1999, pages 153-155, XP000971102 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 cited in the application

2. D1 claiming the same macrocyclic lactones as in the present application, compositions thereof and a method of preventing or treating cancer using optionally an additional

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/05582

compound other than the claimed compounds (claims 7, 18; p. 10, l. 13-20; p. 17, l. 9-37) is novelty-destroying for originally filed claim 19 and new claim 21 (Art. 33(2) PCT).

D2 discloses the isolation of two cytotoxic macrolides, lobatamides A and B (p. 8968, col. 1, l. 1-7).

D3 also shows the isolation of potentially cytotoxic macrolides, namely salicylihalamides A and B, whereas D4 describes two novel compounds CJ-12,950 and CJ-13,357 and their effect in increasing the number of LDL receptors.

In D5 oximidines I and II (Fig. 1) have been found as selective antitumour drugs (p. 154, col. 2, par. 3).

3. The problem to be solved by the present invention could be regarded as finding alternatives to the known vacuolar-type (H⁺) ATPase inhibitors in order to use them in e.g. cancer treatment or other diseases such as osteoporosis.

Since the search has been restricted due to the lack of clarity, an opinion regarding the assessment of inventive step can be given only for the parts relating to new claims 12-17 and 25-30:

There is no prove given in the description as to the effectiveness of the compounds, in other words they are not supported by special embodiments showing the claimed effects. Actually, a conclusion is only made from the fact that the screened substances have fingerprints matching standard agents being known vacuolar-type (H⁺) ATPase inhibitors (in this case concanamycin A). The skilled person would act in the same way by deriving the teaching of D1 without the exercise of inventive skill, in order to screen substances having fingerprints matching to agents having the desired activity. There is a lack of embodiments showing e.g. the inhibition of urinary acidification or bone resorption but only the demonstration of the vacuolar-type (H⁺) ATPase inhibition (ex. 6).

If the effect itself was claimed, i.e. e.g. the inhibition of osteoporosis, and confirmation or sufficient prove of the claimed effects was to be given, claims 12-16 and 25-29 would meet the requirements of Article 33(3) PCT regarding the involvement of an inventive step.

Claims 17 and 30 would not be regarded as inventive due to the relation of angiogenesis to cancer which is also highlighted by the applicant on page 3 of the description.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/05582

4. For the assessment of the present claims 1-17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

1. A lack of clarity concerning the term "vacuolar-type (H⁺) ATPase" and the parameters chosen by the applicant has led to a restricted search (see Search Report).

Furthermore, claims 1-11 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined due to the functional statement "inhibition of vacuolar-type (H⁺) ATPase".

When a claim is directed to a further therapeutic application of a medicament and the condition to be treated is defined in functional terms, the claim can be regarded as clear only if instructions, in the form of experimental tests or any testable criteria, are available from the patent documents or from the common general knowledge allowing the skilled person to recognise which conditions fall within the functional definition and accordingly within the scope of the claim since the claim embraces an undefined number of other not specified conditions all allegedly capable of being treated or prevented by the inhibition of vacuolar-type (H⁺) ATPase.

2. There is a lack of clarity regarding the aromatic ring (mentioned after R³) in claims 1 and 3, and originally filed claim 19. It is not specified which ring is meant, the one in general formula (I) or the aryl of R³, like in the description on page 5.

3. The incorrect dependency to claim 17 in new claim 19 (former claim 24) leads to unclarity regarding the definition of R¹-R³ (R⁶ is correctly dependent on claim 18).

4. The statement on page 91 concerning the "spirit" of the invention seems to imply that the extent of protection may be expanded in some vague way (Guidelines III 4.3a PCT).